Citation:

Howarth NC, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. The association of glycemic load and carbohydrate intake with colorectal cancer risk in the Multiethnic Cohort Study. *Am J Clin Nutr.* 2008 Oct;88(4):1074-82.

PubMed ID: 18842796

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine the risk of colorectal cancer associated wtih glycemic load, carbohydrate, and sucrose and to ascertain whether this risk was modified by sex and ethnicity.

Inclusion Criteria:

- The Multiethnic Cohort Study includes >215,000 participants who were 45 - 75 years old in 1993, residing in Hawaii or Southern California, predominantly of five ethnic groups: African American, White, Latino, Native Hawaiian, or Japanese American

Exclusion Criteria:

- Cohort members outside the five major ethnic groups (n = 13,992)
- Persons whose diets, based on energy and macronutrients from the baseline food frequency questionnaire were deemed implausible (n = 8,264)
- Subjects with a diagnosis of colorectal cancer before the study, identified by self-report or by registry linkages (n = 2,560)

Description of Study Protocol:

Recruitment

Data from the Multiethnic Cohort Study was analyzed for 191,004 participants. The cohort study was designed to examine the association of diet, lifestyle and genetics with the incidence of various types of cancer and other chronic diseases and to compare effects across ethnic groups.

Design: Prospective Cohort Study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Using Cox regression, adjusted relative risks and 95% confidence intervals were calculated for colorectal cancer associated with quintiles of glycemic load, carbohydrate and sucrose
- Glycemic load, carbohydrate and sucrose exposures were adjusted for energy intake by using the residual method
- Differences across ethnic groups in the effects of glycemic load, carbohydrate and sucrose were assessed by likelihood ratio tests comparing models with interactive terms between ethnicity and trend variables, and models with main effects only
- Means were adjusted for age and ethnicity by using ANOVA, and Pearson's correlation coefficient was used to assess association between dietary factors

Data Collection Summary:

Timing of Measurements

- Between 1993 and 1996, participants completed a 26-page mailed self-administered survey instrument that included a comprehensive quantitative FFQ and that assessed demographics, medical history, use of medications and vitamin supplements, family history of common cancers, lifestyle factors such as physical activity and smoking status, and self-reported height and weight; women were also asked about reproductive history and use of hormone replacement therapy
- Participants were followed for 8 years; case ascertainment was complete through December 31, 2002

Dependent Variables

- Colorectal cancer risk: incident colorectal cancer cases identified by record linkage to the Hawaii Tumor Registry, the Cancer Surveillance Program for Los Angeles County, and the California State Cancer Registry, all registries are members of the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute

Independent Variables

- Glycemic load and carbohydrate intake
- Quantitative food frequency questionnaire data was used to assess usual dietary intake over the preceding year
- The quantitative food frequency questionnaire was developed specifically for the study population and was based on 3-day measured food records kept by men and women aged 45 -75 years from each ethnic group, and traditional foods of each ethnic group were also included
- Glycemic index values were assigned to each constituent food or imputed from similar foods

Control Variables

- Energy intake
- Ethnicity
- Age at cohort entry
- Time since cohort entry

- Family history of colorectal cancer
- History of colorectal polyp
- Pack-years of cigarette smoking
- BMI
- Physical activity
- Nonsteroidal anti-inflammatory drug use
- Multivitamin use
- Hormone replacement therapy
- Intakes of red meat, dietary fiber, folate, vitamin D, calcium and alcohol

Description of Actual Data Sample:

Initial N: 215,820 total participants in the cohort

Attrition (final N): After exclusion criteria were applied, 191,004 participants were included in the analysis, 85,898 men and 105,106 women.

Age: 45 - 75 years old in 1993

Ethnicity: see Results

Other relevant demographics:

Anthropometrics

Location: Hawaii and Southern California, United States

Summary of Results:

Key Findings

- Over 8 years of follow-up, 2,379 incident cases of colorectal adenocarcinoma occurred (1,293 men and 1,086 women)
- In multivariate models, relative risks for colorectal cancer decreased significantly with increasing glycemic load in women (RR for the highest versus the lowest quintile: 0.75, 95% confidence interval: 0.57, 0.97, P for trend = 0.02) but not in men (RR = 1.15, 95% confidence interval: 0.89, 1.48, P for trend = 0.19)
- Results for carbohydrates and sucrose were similar
- The inverse association with glycemic load was found in women of all ethnic groups (P for interaction = 0.58)
- In men, an interaction was found between ethnicity and glycemic load (P < 0.01) in that white men had a positive association with increasing glycemic load (RR = 1.69, 95% confidence interval: 0.98, 2.92, P for trend = 00.01), but men of other ethnic groups did not

Relative Risks (95% CIs) of Colorectal Cancer by Quintile of Glycemic Load for Each Ethnic Group

Variables	Q2	Q3	Q4	Q5	P for Trend

Men - African American (n = 166)	1.06 (0.65, 1.75)	1.31 (0.78, 2.21)	1.18 (0.66, 2.09)	1.29 (0.68, 2.44)	0.404
Men - Japanese American (n = 491)	1.11 (0.73, 1.69)	1.13 (0.74, 1.73)	0.92 (0.59, 1.44)	0.95 (0.59, 1.53)	0.399
Men - Latino (n = 172)	0.83 (0.55, 1.24)	1.00 (0.65, 1.54)	1.06 (0.66, 1.71)	1.17 (0.67, 2.03)	0.456
Men - White (n = 259)	0.91 (0.60, 1.38)	1.02 (0.65, 1.62)	1.77 (1.11, 2.80)	1.69 (0.98, 2.92)	0.006
Women - African American (n = 300)	1.02 (0.71, 1.47)	1.05 (0.71, 1.56)	0.93 (0.59, 1.46)	0.74 (0.43, 1.29)	0.507
Women - Japanese American (n = 335)	1.00 (0.56, 1.79)	1.25 (0.72, 2.18)	0.82 (0.47, 1.46)	0.76 (0.42, 1.37)	0.050
Women - Latina (n = 168)	0.96 (0.62, 1.50)	0.84 (0.51, 1.38)	0.48 (0.25, 0.93)	0.75 (0.38, 1.46)	0.107
Women - White (n = 216)	1.00 (0.64, 1.56)	1.05 (0.65, 1.68)	1.18 (0.71, 1.98)	0.68 (0.35, 1.33)	0.594

Other Findings

- For both men and women, white rice was the major contributor to glycemic load
- In both sexes, participants with a higher glycemic load tended to be older, of slightly lower BMI, somewhat more active, and less likely to smoke or consume alcoholic beverages
- Both men and women in the highest quintile of glycemic load compared with the lowest consumed less meat, potatoes, and vegetables but more energy, fiber, fruit, grains and sucrose

Author Conclusion:

In conclusion, contrary to our hypothesis, glycemic load and carbohydrate intake both appear to be protective against colorectal cancer in women after adjustment for potential confounders. This divergence from previous reports linking glycemic load to colorectal cancer through insulin resistance indicates that carbohydrate foods may not all have the same predictive effect on insulin response and, thus, on disease. Further investigation of the glycemic effects of rice-based diets is needed.

Reviewer Comments:

Large multiethnic cohort. Dietary intake only assessed at baseline. Authors note the following limitations:

- *It is uncertain how well the diet and lifestyle data collected at baseline reflect the entire*

follow-up period

- *Residual confounding by lifestyle and dietary factors could not be fully controlled for in the models*
- *Small number of rectal cancer cases in the present cohort may have resulted in lack of power to see relations*
- *Present study required the calculation of glycemic index and glycemic load for each participant; food frequency questionnaire may have skewed the data*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	Yes

3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A

6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	No
7.1.	Were primary and secondary endpoints described and relevant to the question?	No
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	No
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	N/A
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes

	8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
	8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
	8.6.	Was clinical significance as well as statistical significance reported?	Yes
	8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		Yes
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	Yes